IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Kogami et al.	) Group Art Unit:
		) 1626
Appl. No. :	10/523287	)
		) Examiner:
Filed :	February 3, 2005	) Havlin, Robert H
		)
For :	Process for producing n-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine and intermediate	)

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents

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Alexandria, VA 22313-1450

Dear Sir:

I, __ Kenji Kogami _ do hereby declare that:

1. I am one of the inventors of the above-identified application.

2. the experiments given below were carried out under my general direction and supervision.

Experiment

1. Summary and Purpose of Experiment

A (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine was reduced in the presence and absence of a carboxylic acid. The yields of the resulting *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine were compared.

2. Experimental Methods

Test 1

0.836 g (0.005 mol) of (*Z*)-*N*-monomethyl-3-oxo-3-(2-thienyl)propenamine was dissolved in 4.0 g of toluene, and the resulting solution was heated to 50° C. After adding 0.757 g (0.020 mol) of sodium borohydride to the solution, a reaction was carried out at 80° C for 2 hours. The reaction product was measured by HPLC. The reaction mixture was cooled and washed with an aqueous sodium hydroxide solution. The solvent was then distilled off under reduced pressure, and the reaction product was purified using silica gel column chromatography.

Test 2

A test was conducted in the same manner as in Test 1, except that 0.6 g of acetic acid was added to the solution prior to heating a toluene solution of

(*Z*)-*N*-monomethyl-3-oxo-3-(2-thienyl)propenamine to 50° C.

Result

The results of HPLC in Tests 1 and 2 are shown in Table 1.

	A (LC area%)	B (LC area%)
Test 1	1.9	91.0
Test 2	77.5	1.5

* Sensitivity ratio (mol basis) A:B=1:2.2

* A: *N*-monomethyl-3-hydroxy-3-(2-thienyl)propanamine

  B: (*Z*)-*N*-monomethyl-3-oxo-3-(2-thienyl)propenamine

As a result of silica gel column chromatography, the content of *N*-monomethyl-3-hydroxy-3-(2-thienyl)propanamine obtained in Test 1 was as low as 0.026 g (yield: 3%), whereas the content of *N*-monomethyl-3-hydroxy-3-(2-thienyl)propanamine obtained in Test 2 was as high as 0.668 g (yield: 78%).

As is clear from the above, the reduction reaction of (*Z*)-*N*-monomethyl-3-oxo-3-(2-thienyl)propenamine hardly proceeds in the absence of acetic acid (Test 1). In contrast, almost all of the (*Z*)-*N*-monomethyl-3-oxo-3-(2-thienyl)propenamine was reduced in the presence of acetic acid (Test 2), thereby obtaining an *N*-monomethyl-3-hydroxy-3-(2-thienyl)propanamine at an extremely high yield.

Analysis

The results reveal that almost no reduction reaction of (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine occurs in the absence of carboxylic acid, whereas almost all of the (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine was reduced in the presence of carboxylic acid, thereby obtaining an *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine at an extremely high yield.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 30, 2009 Kenji Kogami

Kenji Kogami